Am. Ind. Hyg. Assoc. J. 48(3):208-213 (1987)

A Critical Analysis of the Use of the CFK Equation in Predicting COHb Formation

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Fifteen healthy young males, nine at rest and six at exercise, were exposed to high transient levels of carbon monoxide (CO) to simulate the breathing environment measured in an armored vehicle during weapons firing. Depending on the dosage, the CO exposures raised the subjects' carboxyhemoglobin saturation (%COHb) from 1.7% to 17.3%. The measured %COHb levels compared favorably (regression coefficient, b=1.04) to those predicted by the theoretical model of Coburn *et al.* When the application of this same model by a method proposed by NIOSH was used, however, a significant overprediction was found (b=1.28). It appears that this overprediction results primarily from the omission of water vapor in the lungs when the inspired pressure of CO is considered, and to the use of incorrect values for alveolar ventilation. These results demonstrate the errors that may arise from the incorrect utilization of the equation by Coburn *et al.* and the effect that this may have upon the calculation of the limits for safe occupational exposure to CO.

Introduction

Standards to limit human exposure to carbon monoxide (CO) have focused on occupational exposures where allowable time-weighted averages (TWA) and ceiling concentrations are set.[1] There are instances, however, where people are exposed occupationally or accidentally to high transient concentrations that lie outside these limits. Such exposures to CO are indigenous to military environments as the result of weapons firing within confined spaces. In these instances, it is more appropriate to relate high transient exposures to the resulting carboxyhemoglobin percentage saturation (% COHb) for determination of safe limits. The resulting %COHb during transient exposures to CO — or continuous exposures until a steady-state condition is attained — is sensitive to time through the rate of CO uptake.

A method for predicting %COHb from continuous exposure to CO has been proposed by the National Institute for Occupational Safety and Health (NIOSH).[2] The basis for this method stems from a theoretically-derived equation, CFK (Coburn, Forster and Kane[3]), for predicting the time rate of change of carboxyhemoglobin in man. Although the CFK equation originally was developed for the study of the endogenous production of CO, it has been applied to predict CO uptake from exposures to external sources for subjects both at rest and exercise.[4-9] In some of these cases, %COHb exceeded 20%; in none of these cases was the solution of the CFK equation as proposed by NIOSH tested.

The CFK equation was applied by NIOSH to chronic CO exposure cases under varying levels of respiratory ventilation resulting from physical work. It seemed appropriate, therefore, to use this equation for predicting the rate of CO uptake of an armored vehicle crew in the field. In field studies conducted using armored vehicles, the concentration of CO breathed by the crew and their resultant %COHb were measured. These exposures to CO were transient and peak concentrations approached 4000 parts per million (ppm). The measured %COHb values were consistently lower than those values predicted with the use of the NIOSH solution of the CFK equation. Incorrect values of the inspired concentration of CO and the alveolar ventilation will cause errors in the calculated rate of change of carboxyhemoglobin and therefore in the predicted %COHb before a steady-state condition is attained. Once a steady-state condition is attained, the predicted %COHb is sensitive to the inspired concentration of CO and not to the alveolar ventilation. The hypothesis of this study is that the overpredicted %COHb when the NIOSH solution of the CFK equation is used results from the omission of the water vapor in the lungs when the partial pressure of CO in the inspired gas is considered, and from the use of incorrect values for alveolar ventilation.

If this hypothesis is correct, it points to the misinterpretation of the CFK equation not only by NIOSH, but possibly by others as well. For instance, in Reference 5, the authors explicitly neglect the saturation of the inspired CO. In References 4, 6, 7, 8 and 9, it is not clear whether saturation of the inspired CO was considered. Insofar as alveolar ventilation is concerned, Reference 8 used standard temperature and pressure and dry (STPD) conditions, as explicitly specified by Coburn *et al.*[3] Yet Reference 7 used body temperature and pressure and standard (BTPS) conditions, and References 4, 5, 6 and 9 did not state the condition used.

This study will examine the CFK equation and its parameters and outline a solution that later will be compared to that proposed by NIOSH. Predicted values of %COHb by both methods are compared to measured values in laboratory experiments where subjects, both at rest and exercise, were exposed to high transient levels of CO. To further test the authors' hypothesis, prediction with the use of the NIOSH method of solution corrected only for the saturation of the inspired CO and for alveolar ventilation under STPD conditions are presented in the discussion.

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Theoretical Considerations

The rate of change of (COHb) as derived by Coburn *et al.*[3] is

$$\frac{d(COHb)}{dt} = \frac{\dot{V}_{CO}}{V_b} + \frac{1}{V_b\beta}\left(P_{I_{CO}} - \frac{(COHb)\overline{PcO_2}}{(O_2Hb)M}\right). \quad (1)$$

where

$$\beta = \frac{1}{D_L} + \frac{(P_B - 47)}{\dot{V}_A} \quad (2)$$

and, where (COHb) is the concentration of CO bound to hemoglobin (mL STPD mL^{-1} blood);

$\dot{V}_{CO}$ is the rate of the endogenous production of CO (mL STPD min^{-1});

V_b is the effective blood volume (mL);

$P_{I_{CO}}$ is the saturated inspired CO pressure (mmHg);

$\overline{PcO_2}$ is the mean O_2 tension in the pulmonary capillary blood (mmHg);

M is the Haldane ratio of the affinity of blood for CO to that for O_2;

(O_2Hb) is the concentration of O_2 bound to hemoglobin (mL STPD mL^{-1} blood);

D_L is the pulmonary diffusing capacity of CO (mL STPD min^{-1} mmHg^{-1});

P_B is the barometric pressure (mmHg);

and $\dot{V}_A$ is the alveolar ventilation (mL STPD min^{-1}).

It is noted that the parameters of the CFK equation are defined in units under STPD conditions. The CFK equation can, however, be solved under BTPS conditions; but whatever condition is used, it must be used consistently in all the parameters of the equation. As pointed out earlier, it is not clear whether this has been the case in some previous studies.

Coburn *et al.*[3] solved Equation 1 analytically by assuming a constant value of (O_2Hb). The assumption of a constant (O_2Hb) was adopted by NIOSH[2] and others[5,7] and used in this study to evaluate the solution by NIOSH. When the inspired CO concentrations are large enough to cause significant increases in the value of (COHb), however, the decrease of (O_2Hb) must be considered. This decrease can be approximated by[4]

$$(O_2Hb) = 1.38\ H_b - (COHb), \quad (3)$$

where H_b is the hemoglobin concentration (g Hb 100 mL^{-1} blood). With this substitution, Equation 1 becomes nonlinear and can be solved numerically. Tyuma *et al.*[8] presented one such solution; however a cumbersome iterative procedure was required to determine the final (COHb) value.

Alternatively, the solution of (COHb) from Equation 1 reported by Peterson and Stewart[4] involved a trial and error method. Although their method gave a more accurate prediction of the final value of (COHb) than by the assumption of a constant value of (O_2Hb), it did not take into account the cumulative effects of a changing (O_2Hb) values with time. Instead, it considered only the instantaneous value of (O_2Hb) at the end of the exposure. This procedure causes a slight underprediction in the final value of (COHb).

Numerical integration can be used to solve the nonlinear form of Equation 1 so that the changing value of (O_2Hb) with the time can be taken into account. Although numerical integration is by its nature an approximation, the inherent error when this procedure is used can be minimized. In this study, the fourth order Runge-Kutta method was used to solve Equation 1 with a time step sufficiently small so that further refinement produced changes much less than the resolution of the %COHb measurement.

Materials and Methods

Two series of experiments were designed to simulate resting and working conditions during the operation of an armored vehicle and the resultant high transient exposure to CO from actual firing conditions in the vehicle. In the first series of experiments, nine young healthy males† at rest, were exposed to varying concentrations of CO over a 4.5-min period. The exposure was stepwise-symmetric beginning with 500 ppm CO for 60 sec, followed by steps of 1000, 2000, 4000, 2000, and 1000 ppm CO for 30 sec each and ending with 500 ppm CO for 60 sec. This transient exposure gave the subjects a nominal CO dosage of 6000 ppm·min.

For the second series of experiments, six subjects† underwent cycles of exercise and rest. Exercise was performed on a bicycle ergometer set at 135 W. Each exercise period lasted for 5 min and was preceded by a warm-up at 75 W for 30 sec. The resting period between exercise was 15 min. Three subjects went through two exercise rest cycles, whereas the others went through three cycles. The shaded regions in Figure 1 represent the time when the subject was given CO. Subjects RV, DH, and JG were given CO at the nominal level of 1000 ppm during the full 5 min of exercise to produce target CO dosages of 5000 ppm·min. For subject RP, the first and last dosing periods were 4.5 min long to produce target CO dosages of 4500 ppm·min. For subjects MB and RE, CO was given at the nominal level of 4000 ppm for 75 sec (target CO dosage of 5000 ppm·min), 3 min after the start of exercise.

During both series of experiments, each subject was fitted with an oro-nasal aviator's mask (MSA Type A13A) that was connected to an aviator's pressure demand regulator (ARO Model MD2). The inlet of the regulator was connected to a valve that permitted rapid switching between room air and the air-CO mixture used during the experiment. The nominal concentrations of CO used were 500, 1000, 2000 and 4000 ppm balanced with ultra-high pure dry air. The actual ambient concentration of CO breathed by each subject was measured by sampling the air before inspiration and analyzing it by infrared spectrometry (Infra-Red Industries Inc., CO Analyzer Model 7733). The total dosage of CO received, in ppm·min, was determined by integrating the measured CO concentration over the exposure period. These values are listed in Table I for the subjects at rest and given above the shaded regions in Figure 1 for the subjects at exercise.

†All subjects gave informed consent and were screened for suitability in accordance with DCIEM's Human Ethics Committee requirements.

TABLE I
Measured and Predicted COHb for Resting Subjects

Subject	CO Dosage (ppm·min)	% COHb				
		Measured		Predicted Post		
		pre	post	DCIEM	NIOSH	NIOSHc
DB	6123	4.7	6.5	7.3	7.4	6.9
MB	6123	4.8	7.9	7.2	7.5	6.9
HD	5960	5.4	7.8	8.0	8.0	7.5
RS	6211	3.4	5.4	5.3	6.1	5.6
CR	6100	2.1	4.2	4.1	4.8	4.3
RB	6111	0.7	2.8	2.8	3.4	2.9
LP	6190	0.5	2.2	2.7	3.3	2.8
RV	5887	0.4	2.6	2.4	3.1	2.5
DT	6037	1.4	3.7	3.7	4.1	3.6
Mean difference between pre and post values ±SD			2.2±0.4	2.2±0.3	2.7±0.1	2.2±0.1

Blood samples (3 mL) were drawn from a superficial vein of the nondominant arm prior to each exposure to CO and between 2 to 4 min after each exposure. Blood carboxyhemoglobin concentrations were measured by a gas chromatographic technique after the method of Collison *et al.*[10] The gas chromatograph (Carle Industries Inc., Model 211) was fitted with a palladium catalyst converter and FID detector. A sample of the head space gas from the reaction vial was delivered to the column through a gas sampling loop of 0.10 mL.

Results

The measured and predicted %COHb for the nine subjects at rest are listed in Table I. Predicted values are listed in accordance to the solutions of the CFK equation utilized by NIOSH and the authors (DCIEM). These solutions will be discussed later. There is disagreement between the predicted increases in %COHb and the measured increases based on the NIOSH solution of the CFK equation. On the other hand, no difference was found between the measured increases in %COHb and the predicted increases for the authors' solution of the CFK equation.

The measured and predicted results for the six subjects who underwent exercise/rest cycles are shown in Figure 1. In every case, the predictions obtained when the NIOSH solution of the CFK equation was used exceeded the measured values. For the authors' solution, the predictions sometimes exceeded and at other times underpredicted the measured values. The apparent linearity of the predicted time course of %COHb is characteristic of both solutions for up to 20% saturation.

Linear regressions of all of the post-exposure results (*i.e.*, excluding pre-exposure) for both resting subjects and exercise/rest subjects are shown in Figures 2 and 3. Overall, the authors' application of the CFK equation resulted in predicted increases in %COHb that agreed much more closely with the measured increases than did those of the NIOSH solution with regression coefficients of 1.04 and 1.28, respectively.

Discussion

To distinguish the authors' method of solution of the CFK equation from the one proposed by NIOSH, Table II lists all the parameters of the CFK equation and the values assigned to them by both NIOSH and the authors. The first three of these parameters — $\dot{V}_{CO}$, $\dot{V}_A$, and D_L — were not measured for the experiment described here. Instead, they were assigned the same numerical values as assumed by NIOSH.[2]

The prediction of the rate of change of [COHb] is dependent upon the assignment of the level of activity of the subject. Both values of the parameters D_L and $\dot{V}_A$ were chosen on this basis. For those subjects at rest, the NIOSH values for sedentary activity were chosen. To establish the level of activity for those subjects at exercise during bicycle ergometry, the subject's energy expenditure was determined through interpolation from a table of exercise energy coversions.[11] In terms of oxygen consumption ($\dot{V}_{O_2}$), estimated values ranged between 1.99 and 2.02 L/min. According to the physiological classification of work,[12] a $\dot{V}_{O_2}$ of 2.0 L/min represents the transition from very heavy to extremely heavy work. On this basis, the NIOSH values for heavy work were selected to represent the subject's level of activity during exercise.

The NIOSH values of $\dot{V}_A$, 6000 and 30 000 for subjects at rest and heavy work, respectively, are within the physiological range under BTPS conditions, but they are about 21% higher than their equivalent STPD values. The consequence

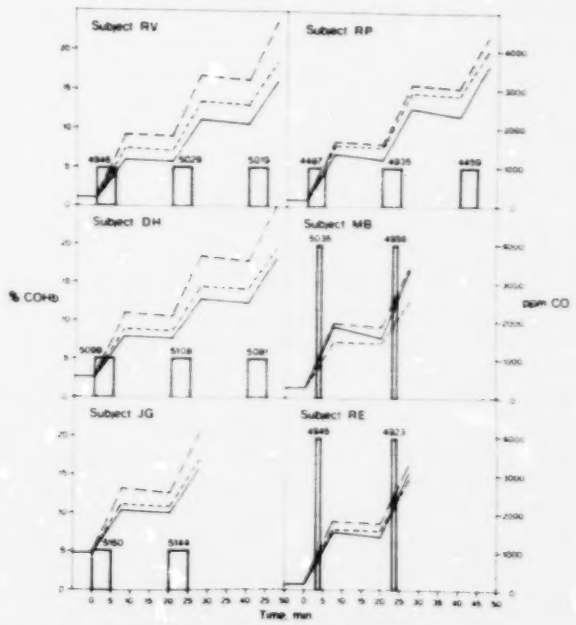

Figure 1 — Measured and predicted %COHb for subjects who underwent exercise/rest cycles. The shaded regions represent the time when the subject was given CO, and the numbers above these regions indicate the CO dosage in ppm·min. The solid lines represent the measured %COHb, the dashed lines represent the predicted %COHb according to the authors' solution of the CFK equation, and the dashed-dot lines represent the predicted %COHb according to the solution proposed by NIOSH.

of using overly high values of $\dot{V}_A$ in the CFK equation is to overpredict the rate of change of [COHb]. For example, a 21% increase in $\dot{V}_A$ will cause an overprediction in the rate by about 12% to 16% depending on the activity level of the subject (a higher level of activity will tend to lessen the overprediction). If a steady-state level is not attained during the exposure, as in the cases investigated here, then the final [COHb] also will be overpredicted by about the same percentage. The steady-state level of [COHb] has a weak dependence upon $\dot{V}_A$ and is governed largely by the inspired concentration of CO.[3] According to the authors' hypothesis, it was assumed that the NIOSH values of $\dot{V}_A$ pertain to BTPS conditions and so the appropriate conversion to STPD conditions was made for the authors' application of the CFK equation.

For the remaining parameters in the CFK equation, the authors' values differed from those used by NIOSH as follows. NIOSH assigned the value of 218 to the Haldane ratio, M. Recent estimates[9] place the value of this parameter closer to 240, which was adopted in the authors' application. A larger value of M results in a lower rate of increase of [COHb].

The effective volume of blood, V_b, used by NIOSH was 5500 mL. In this application of the CFK equation, blood volume was estimated from[13]

$$V_b = 0.0003669H^3 + 32.19\ W + 604. \quad (4)$$

where H is the height (cm) and W is the weight (kg) of the subject. The mean blood volume thus calculated for the subjects was 5222 mL. Although body stores other than blood could absorb CO, information was not available on either the extent or the rate of this absorption for human

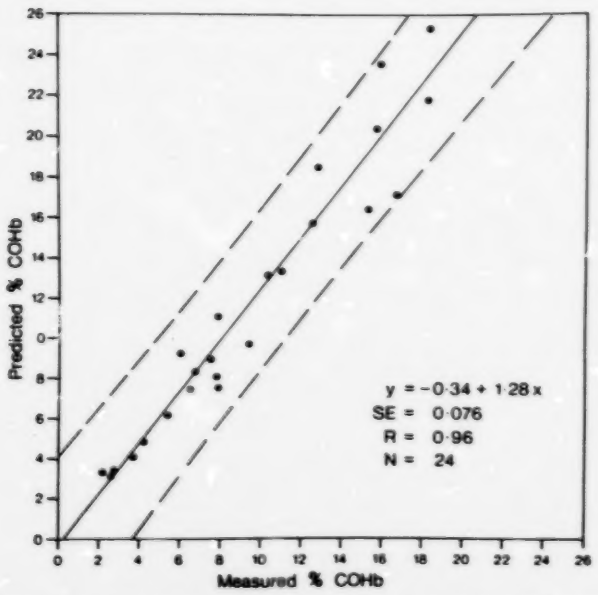

Figure 2 — Linear regression of the predicted %COHb according to the solution of the CFK equation proposed by NIOSH for all the post-exposure data. The dashed lines indicate the 95% confidence limits for the predicted values.

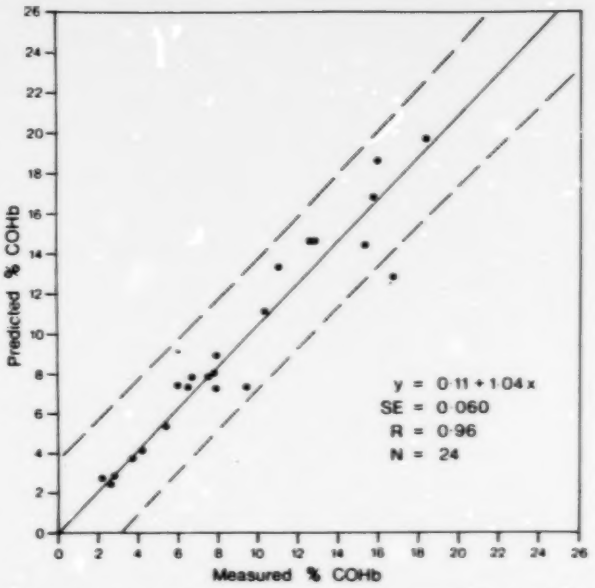

Figure 3 — Linear regression of the predicted %COHb according to the authors' solution of the CFK equation for all the post-exposure data. The dashed lines indicate the 95% confidence limits for the predicted values.

subjects; therefore, this effect was not taken into account. If this effect were taken into account by use of a higher estimate of the effect blood volume, a lower rate of increase of [COHb] and thus closer agreement with the measured values would have been achieved. In fact, use of the V_b value assumed by NIOSH in the authors' solution of the CFK equation would have lowered the authors' predicted rate of [COHb] increase by about 5%. It is emphasized that only the rate of change of [COHb] and not the steady-state value of [COHb] is dependent upon V_b.[3]

The mean tension of O_2 in the pulmonary capillary, $\overline{PcO_2}$, is assumed in the solution used by NIOSH to be 100 mmHg. The authors, instead, determined this value from[13]

$$\overline{PcO_2} = P_{I_{O_2}} - 49. \quad (5)$$

where $P_{I_{O_2}}$ is the inspired O_2 pressure (mmHg). For the experimental conditions described here, this value was determined by

$$P_{I_{O_2}} = 0.21\ (P_B - 47). \quad (6)$$

where the barometric pressure, P_B, was measured. The difference, however, between the value of $\overline{PcO_2}$ used by NIOSH and that determined through Equation 5 was typically less than 3 mmHg.

The saturated inspired CO pressure was determined by

$$P_{I_{CO}} = \left(\frac{ppmCO}{10^6}\right)(P_B - 47), \quad (7)$$

where ppm CO is the concentration of CO in the dry component of the ambient gas. The solution used by NIOSH assigns the value of $P_{I_{CO}}$ as the pressure of CO in the ambient

TABLE II
Comparison of Parameter Values Used in the CFK Equation

Parameter		NIOSH[1]	DCIEM
$\dot{V}_{CO}$		0.007 mL/min	0.007 mL STPD/min
$\dot{V}_A$	sedentary	6000 mL/min	6000 mL BTPS/min
	heavy work	30 000 mL/min	30 000 mL BTPS/min
D_L	sedentary	30 mL/min/mmHg	30 mL STPD/min/mmHg
	heavy work	60 mL/min/mmHg	60 mL STPD/min/mmHg
M		216	240
V_b		5500 mL	0.0003669 H^3 + 32.19W + 604 mL
$P_{I_{CO}}$		ppmCO/1316	$(P_B\text{-}47) \times$ ppmCO/10^6 mmHg
$P_I O_2$		100 mmHg	0.21 $(P_B\text{-}47\text{-}P_{I_{CO}})$-49 mmHg
(O_2Hb)		0.2 mL/mL blood	1.38 H_b - [COHb] mL STPD/mL blood
P_B		760 mmHg	measured

[1]Units shown as given in Reference 2.

gas breathed; the factor 1316 shown in Table II assumes a barometric pressure of 760 mmHg. This factor fails to take into account the reduction of the inspired gas pressure by the presence of water vapor in the lungs, *i.e.*, the saturated condition. This error causes about a 7% overprediction in the rate of increase of [COHb]. In addition, this error also will cause the same degree of overprediction in the steady-state value of [COHb].

The overprediction caused by treating [O_2Hb] as constant will not be large unless the subject has a high initial [COHb] value. Nevertheless, in the authors' solution of the CFK equation, [O_2Hb] was corrected for the presence of [COHb] by applying Equation 3. The hemoglobin concentrations, H_b, used to make this correction, was measured from the same blood samples used to determine [COHb]. This approach was necessary to account for hemoconcentration, which occurs in acutely exercised subjects.

As stated earlier, the solution used by NIOSH assumes a barometric pressure of 760 mmHg. In the authors' solution of the CFK equation, P_B was measured so that the correct inspired O_2 and CO pressures could be evaluated (see Equation 6 and 7) and so that the conversion factor — (273/310)(P_B - 47)/760 — could be applied to determine the STPD values of $\dot{V}_A$.

Differences in the values of PcO_2, [O_2Hb], and P_B between the two solutions of the CFK equation by NIOSH and the authors are too small to account for their differences in the predicted increase of [COHb]. The difference in the value of V_b used in the authors' solution of the CFK equation and that used by NIOSH also cannot account for the disparity in the predicted COHb since use of the same value would widen the disparity, as already pointed out. Instead, the difference in the predicted increases in [COHb] that was found between the two solutions leaves in doubt the values of $P_{I_{CO}}$ and $\dot{V}_A$ assigned by NIOSH. The amount of overprediction because of incorrect values of these parameters also has been noted. Coupled together, they can account for an overprediction of the increase of [COHb] by about 21% before a steady-state is attained.

To test whether the NIOSH solution would work if only the parameters $P_{I_{CO}}$ and $\dot{V}_A$ were corrected as implied above, new predictions (designated as NIOSHc) were made with use of the NIOSH method of solution with the following corrections. First, $P_{I_{CO}}$ was determined by

$$P_{I_{CO}} = \text{ppm [CO]} \ 1403. \qquad (8)$$

which still assumes a barometric pressure of 760 mmHg but now takes into account the saturation of the inspired CO. Second, the $\dot{V}_A$ values for sedentary and heavy work were readjusted from 6000 and 30 000 (assuming BTPS values) to 4957 and 24 786 (equivalent STPD values), respectively. As a result of these corrections, no difference was found between the predicted and the measured results for the nine subjects at rest (see Table I). A linear regression of all the post-exposure results (resting plus exercise rest subjects) indicates a much better agreement than obtained previously ($y = -0.11 + 1.09x$; SE = 0.064; R = 0.96; N = 24). In fact, a comparison with the regression coefficient obtained with the NIOSH solution without any correction (*i.e.*, b = 1.28) indicates that the uncorrected version overpredicts the final [COHb] by about 19%, which is consistent with the above theoretically-estimated overprediction of about 21% in the increase of [COHb]. Closer agreement with the measured result could be obtained further by the use of an M value of 240 instead of 214. In fact, use of the higher value would produce a result very close to the authors' solution of the CFK equation. In essence, the differences in prediction between the two solutions lie primarily with the parameters and not with the method of calculation, *i.e.*, numerical *vs.* analytical. Numerical integration of the CFK equation, however, can be expected to add increasingly to the predictive power as the level of %COHb increases.

The corrected version of the NIOSH solution, changing only $P_{I_{CO}}$ and $\dot{V}_A$, also can be tested against the previously measured data of Stewart *et al.*[14] Thirteen experiments were carried out in which transient exposures to CO were given to resting subjects. These exposures, which varied in duration and concentration, resulted in increases in %COHb from 3.2% to 15.2%. A sedentary level of activity (see Table II) is assumed for these subjects. When the original NIOSH solution of the CFK equation is applied, the predicted increases in %COHb are considerably larger than the measured values, but when the modified version is applied, the difference is small.

The overprediction of the rate of change of carboxyhemoglobin and thus the %COHb before steady-state is reached by the NIOSH solution primarily is due to incorrect values of $P_{I_{CO}}$ and $\dot{V}_A$. This also applies to the elimination of CO when breathing no CO; however, in this circumstance the %COHb will be underpredicted until a steady-state condition is reached. According to NIOSH,[2] "The recommended TWA standard of 35 ppm CO is based on a COHb level of 5%, which is the amount of COHb that an employee engaged in sedentary activity would be expected to approach in eight hours during continuous exposure." According to the authors' modification of the NIOSH solution (which takes into account the presence of water vapor in the lung and uses a sedentary $\dot{V}_A$ = 6000 mL BTPS/min), the equivalent TWA exposure would be 43.5 ppm CO.

Conclusion

The solution of the CFK equation by NIOSH overpredicts the rate of change of carboxyhemoglobin. The reason for the overprediction lies primarily with the values of $P_{I_{CO}}$ and $\dot{V}_A$ that were assigned to these parameters. The value of $P_{I_{CO}}$ used in the solution by NIOSH does not account for the presence of water vapor in the lungs, and it also appears that the values of $\dot{V}_A$ were given for BTPS conditions instead of STPD conditions. The corrected version of the NIOSH solution with the above changes [setting $P_{I_{CO}}$ = ppm (CO) 1403 and using $\dot{V}_A$ = 4957 and 24 786 mL STPD/min for rest and heavy exercise, respectively] improves the prediction of %COHB resulting from high transient exposures for subjects both at rest and exercise. In the use of the CFK equation, it is essential that the parameters be defined clearly to ensure conformity to the units assigned by the original authors.

Acknowledgment

The authors acknowledge the advice of F. Buick, J.A.G. Porlier, B.E. Rodden, W.D. Fraser and R.Y. Nishi of DCIEM in the preparation of this paper. DCIEM Research Paper 86-P-46.

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24 September 1985; Revised 12 August 1986